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Risk assessment of formaldehyde

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Abstract

In April 1987, the Environmental Protection Agency (EPA) issued the "Assessment of Health Risks to Garment Workers and Certain Home Residents from Exposure to Formaldehyde" in which formaldehyde was classified as a carcinogen and an irritant to the eyes and respiratory tract. A quantitative risk assessment for cancer was presented. A more current document, a draft released in 1991, incorporates some additional data on the epidemiology and toxicology of formaldehyde that the EPA has received since completion of the earlier assessment, and examines the impact of this information on the estimates of health risks following exposure to airborne formaldehyde. For noncancer effects, the new data support earlier conclusions with regard to the irritant effects of formaldehyde and the dose–response gradient for these effects. The cancer assessment incorporates the use of a molecular dosimeter for the derivation of risk estimates. Tissue levels of this dosimeter, a covalent cross-link product of formaldehyde and DNA-protein (DPX), are available from rats and monkeys. The risk estimates obtained with this dosimeter are considerably lower than those obtained by conventional approaches.

1. Background

A report completed in 1987, "Assessment of Health Risks to Garment Workers and Certain Home Residents from Exposure to Formaldehyde" [1], examined the noncancer and cancer effects associated with formaldehyde exposure. The major noncancer human health effects posed by inhalation exposure to formaldehyde were sensory irritation and cellular changes to nasal epithelium. EPA's conclusions on the noncancer effects associated with exposure to formaldehyde were based mainly upon already-existing reviews by the National Research Council [2],

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Consensus Workshop on Formaldehyde [3], and Interagency Risk Management Council [4].

Considerable evidence was also available for the carcinogenicity of formaldehyde in animals exposed by inhalation. This evidence included the increased incidence of a rare malignant tumor, nasal squamous cell carcinoma, in two species (rats and mice), and in both sexes of two rat strains (Fischer 344 and Sprague–Dawley), in multiple inhalation experiments at high concentrations.

In 1987, EPA also reviewed 28 epidemiologic studies and concluded, based upon EPA's Guidelines for Carcinogen Risk Assessment [5], that 'limited' evidence existed for an association between formaldehyde and human cancers. The epidemiologic studies were considered inadequate for quantitative risk assessment. Therefore, the quantitative risk assessment of formaldehyde reported in 1987 was based on rat bioassay data, in which nasal squamous cell carcinoma incidence were increased with increasing formaldehyde levels in both males and females.

The Office of Pollution Prevention and Toxics (OPPT) conducted a review of epidemiologic and toxicological data developed since the release of EPA's "Assessment of Health Risks to Garment Workers and Certain Home Residents from Exposure to Formaldehyde" [1]. The 1991 draft assessment document [6] incorporates this newer information and evaluates the potential human health risks due to inhalation of formaldehyde vapor. The original conclusions reached with respect to noncancer effects were sustained in the most recent assessment [6]. The present article summarizes the major findings pertaining to the cancer risk case in this updated risk assessment [6] of formaldehyde[1].

2. Carcinogenic effects

EPA has classified formaldehyde as a "Probable Human Carcinogen" (Group B1) under its Guidelines for Carcinogen Risk Assessment [1, 5]. This classification is based on:

- limited evidence of carcinogenicity in humans;
- sufficient evidence of carcinogenicity in animals; and
- additional supportive evidence (i.e. mutagenicity, structure-activity, and mechanistic considerations)

2.1. Studies of humans

Based upon a review of epidemiologic studies, EPA's 1987 document concluded that 'limited' evidence existed that formaldehyde may be a carcinogen in humans [1]. The evidence for potential human carcinogenicity associated with formaldehyde

[1] The updated assessment, "Formaldehyde Risk Assessment Update", 11 June 1991, was reviewed by the EPA's Science Advisory Board in July 1991. The document is publicly available from the OPPT Risk Management (RM) Administrative Record: TSCA Public Docket Number AR-127.

exposure rests heavily on associations with cancers of the nasal cavity and sinus and of the nasopharynx, and to a small degree on observations of elevated risks of lung cancer from combined formaldehyde and particulate exposures. Additional studies were reviewed in the updated assessment [6]. The studies released since 1987 support the initial conclusions drawn by EPA [1]. Although the common exposure in the reviewed studies was to formaldehyde, possible exposure to other agents (e.g. particles) may contribute to the findings of excess site-specific cancers. In addition, excesses in nasopharyngeal, nasal and sinus cavity cancers are based on a small number of deaths. Thus, the epidemiologic evidence is called 'limited'[2] rather than 'sufficient'.

2.2. Studies in animals

Based upon a review of studies released through 1987 [7–9], EPA [1] concluded that there is 'sufficient' evidence of carcinogenicity[3] of formaldehyde in animals [1]. This conclusion is based on the induction by formaldehyde of an increased incidence of a rare type of malignant tumor (i.e., nasal squamous-cell carcinoma) in both sexes of rats, in multiple inhalation experiments, and in multiple species (i.e., rats and mice). In these long-term laboratory studies, tumors were not observed beyond the initial site of nasal contact. Subsequent reports [1, 6] have confirmed the carcinogenicity of formaldehyde in rats.

In contrast to the inhalation data, results obtained from several carcinogenicity studies with formaldehyde given to rats in drinking water provide only suggestive evidence [6] for carcinogenic potential via the oral route. The target tissue in these studies was the forestomach, which is consistent with observations from the inhalation studies in that tumors develop at the site of initial contact. In tumor promotion studies, formaldehyde enhanced the tumor response in mouse skin, rat trachea, and rat stomach indicating that formaldehyde has tumor promotion potential at least in some tissues [6].

2.3. Additional supportive evidence

Tests for point mutations, numerical and structural chromosome aberrations, DNA damage/repair, and in vitro cell transformation provide evidence for the potential mechanisms of carcinogenicity. Formaldehyde is mutagenic in numerous bacterial

[2] EPA's Guidelines for Carcinogen Risk Assessment define limited evidence of carcinogenicity in humans as indicating that "...a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded".

[3] EPA's Guidelines for Carcinogen Risk Assessment define sufficient evidence of carcinogenicity from studies in experimental animals as indicating that "...there is an increased incidence of malignant and benign tumors: (a) In multiple species or strains; or (b) in multiple experiments, preferably with different routes of administration or using different dose levels; or (c) to an unusual degree with regard to incidence, site or type of tumor, dose–response effects, as well as information from short-term tests or on chemical structure."

test systems and test systems using fungi and insects (Drosophila). It transforms cells in culture and causes DNA cross-linking, sister chromatid exchanges (SCE) and chromosome aberrations. In addition, formaldehyde has been shown to bind with DNA and with proteins both in vivo and in vitro. Its ability to interfere with DNA repair in human cells has also been shown. Mutagenicity data obtained since the 1987 assessment confirm the original conclusions [6].

3. Quantitative risk assessment

Cancer risk estimates were derived by modeling data obtained from studies in animals.

3.1. Cancer risk assessment

As detailed in EPA [1], the Kerns et al. study in rats [7] was selected as the best study for cancer risk extrapolation. This study was well designed, well conducted, included multiple doses, and used a large number of animals per dose. The Agency determined [1] that insufficient information was available at present to propose an extrapolation model for formaldehyde different from the linearized multistage procedure recommended by EPA's Guidelines for Carcinogen Risk Assessment [5].

Molecular dosimetry experiments attempting to relate ambient exposures to formaldehyde with tissue-specific levels of formaldehyde-DNA adducts as DNA-protein cross-links (DPX) were available before completion of the 1987 assessment [10]. In that analysis, however, EPA [1] used the administered dose to calculate carcinogenic risk from formaldehyde exposure because of perceived deficiencies in experimental design in the DPX dosimetry approach. Recent evidence with an improved experimental technique indicates that the use of DNA-protein cross-links as a measure of intracellular dose may provide a better indicator of target tissue exposure than would airborne formaldehyde levels [11]. Accordingly, the updated assessment makes use of these dosimetry data. The use of an intracellular dosimeter (DPX) in the derivation of risk estimates would reflect the impact of both mucociliary clearance and metabolism, whose combined influence effectively reduces the amount of formaldehyde available to the nasal epithelial cells. Particularly at low dose levels, much of the inhaled formaldehyde is not available to interact with cellular macromolecules as it is rapidly cleared by the mucociliary system and oxidative metabolism. At sufficiently high exposure concentrations the detoxification mechanisms become overwhelmed, making a greater amount of formaldehyde available for interactions with DNA and other cellular macromolecules. DPX formation appears to increase nonlinearly with increasing airborne exposure concentrations (Fig. 1) in a manner similar to the observed carcinogenic response in the rat cancer bioassay (Fig. 2). These findings suggest possible saturation of detoxification processes at high formaldehyde concentration. The conclusion derived from the above discussion is that the use of airborne concentration in the derivation of risk estimates would, by ignoring important contributions

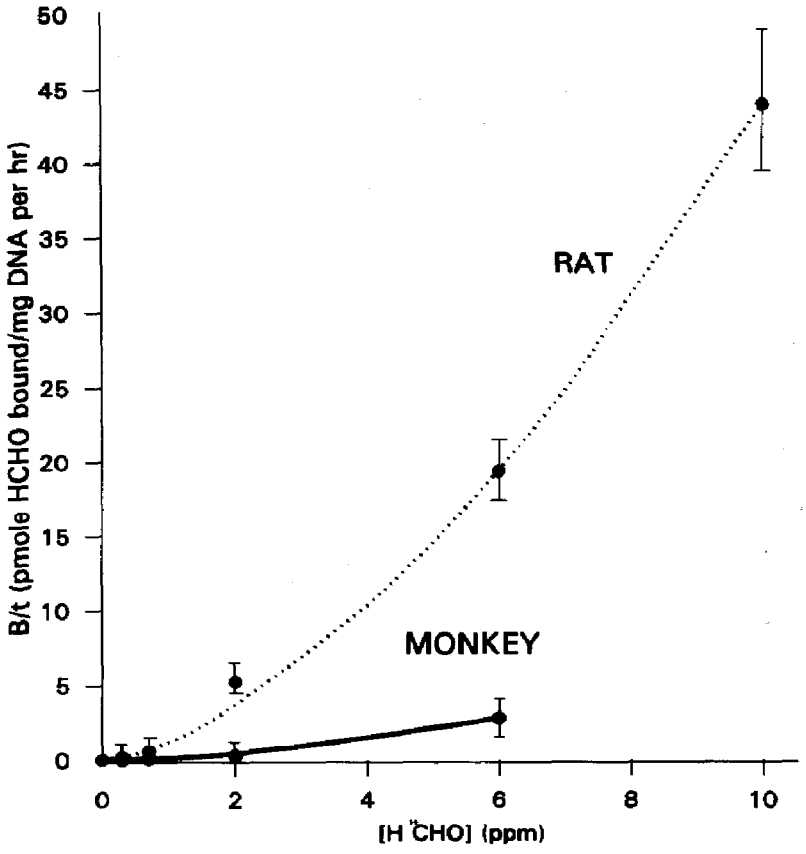

Fig. 1. Formation of DNA-protein cross-links in the turbinates and anterior nose of F-344 rats and rhesus monkeys exposed to $H^{14}CHO$.

from detoxifying processes, lead to an overestimate of intracellular exposure and concomitant risk.

While formation of DPX may lead to a number of genotoxic effects, its role, if any, in the induction of nasal cancer is not completely understood. The authors recognize that the available DNA-binding data are derived from acute or subacute exposure. The latter may either underestimate or overestimate binding levels under chronic exposure conditions where cell proliferation may be significant, particularly at high exposure concentrations. The argument for the use of DPX as a surrogate dose is that this measure provides an index of the area under the curve of a reactive formaldehyde species in the target cells, both in rats and other species [6, 12]. This argument applies whether DPX are mechanistically involved in the carcinogenic process or are simply an indicator of intracellular exposure.

Although toxicological studies on formaldehyde have shown that adverse effects are a function of exposure, there is increasing evidence that toxicity is associated with the intensity of exposure more closely than with total, cumulative, daily dose. Table 1 illustrates a comparison of the effect of dose rate versus total administered dose. Inhalation exposure to a low level of formaldehyde for a long duration of daily exposure (1 ppm for 22 h) over the course of 6 months does not cause lesions in the rat

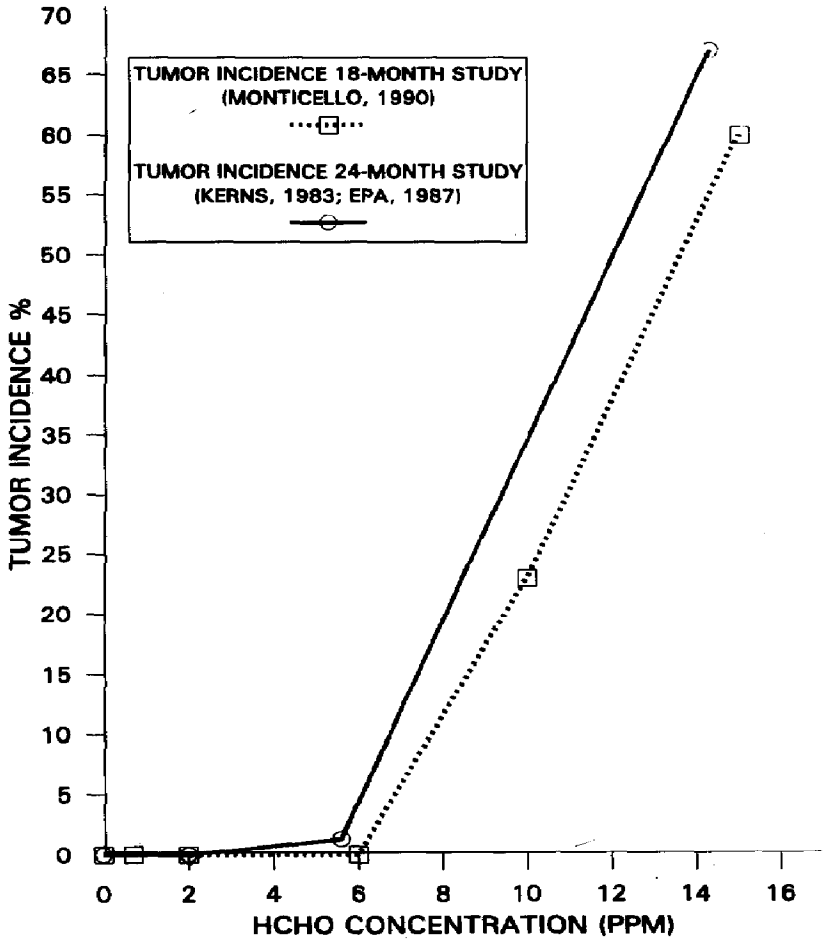

Fig. 2. Formaldehyde tumor incidence (rat).

nose [13]. In contrast, subchronic or chronic inhalation exposure to higher formaldehyde concentrations (2–4 ppm) but with a shorter duration of daily exposure (6 h) produces varying degree of nasal damage in rats [7]. Similar observations are found in a recent subchronic study showing that cell proliferation and nasal damage are only seen with the animal group treated intermittently to high formaldehyde concentration (intermittent exposure for a total of 4 h at 4 ppm). No responses are found in animals receiving the same total daily dose at a lower concentration (2 ppm for 8 h) [14]. All these findings emphasize that the intensity of exposure to airborne formaldehyde is an important exposure parameter and imply that the utilization of lifetime average daily concentrations for risk quantification purposes may overestimate risk potential by lowering the exposure concentration at which adverse effects are expected.

The updated risk assessment [6] incorporated a number of modifications that included the following: (1) the use of GLOBAL86 (as opposed to GLOBAL83) which contains EPA's current interpretation of the linearized multistage procedure; (2) the use of an intracellular dosimeter, DPX binding data, instead of airborne

Table 1
A comparison of dose rate versus total dose in eliciting biological responses in test animals

Experiment	Exposure rate		Total exposure (Ct) (ppm h/day)	Biological response
	Duration	Intensity		
Kerns et al. [7]	6 h/d 5 d/w	2 ppm	12	Nasal passage lesions (squamous metaplasia)
Rusch et al. [13]	22 h/d 7 d/w	1 ppm	22	None
Wilmer et al. [14]	30 min 8 h/d	intervals 4 ppm	16	Cell proliferation/ nasal lesions
	Constant 8 h/d	2 ppm	16	None

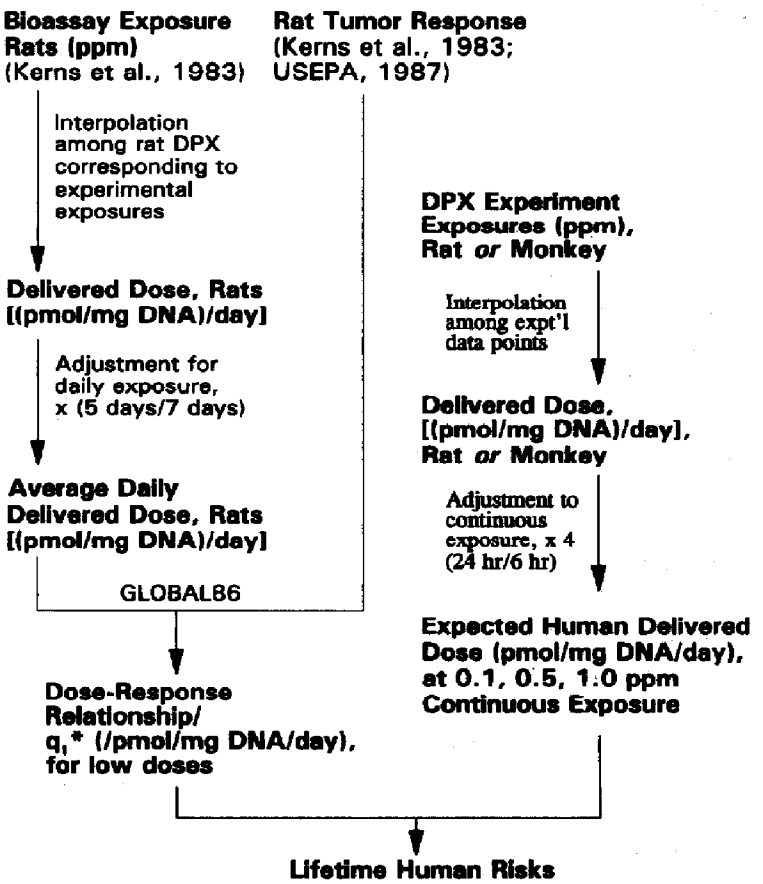

Fig. 3. Steps in the use of DPX as dosimeter.

Table 2
Comparison of estimates of upper bounds (and maximum likelihood estimates) of human lifetime carcinogenic risk associated with lifetime continuous daily exposure to formaldehyde

Exposure rate (ppm)	1987 Risk estimates[a]	1991 Risk estimates[b]	
		Monkey-based	Rat-based
0.1	2×10^{-3} (5×10^{-7})	3×10^{-5} (4×10^{-7})	3×10^{-4} (3×10^{-5})
0.5	8×10^{-3} (5×10^{-4})	2×10^{-4} (1×10^{-5})	3×10^{-3} (1×10^{-3})
1.0	2×10^{-2} (1×10^{-2})	7×10^{-4} (1×10^{-4})	1×10^{-2} (1×10^{-2})

[a] Estimated using 1987 inhalation unit risk 1.6×10^{-2}/ppm.
[b] Incorporated monkey or rat dosimetry data.

concentrations of formaldehyde; and (3) the replacement of lifetime average daily exposure adjustments used in 1987 [1] with daily accumulated DPX loadings. These are illustrated in Fig. 3.

The unit risk estimates obtained as described above are shown in Table 2. The data in Table 2 include the risk estimates derived in 1987 [1] utilizing airborne formaldehyde concentrations.

4. Discussion

Toxic effects from exposure to formaldehyde appear to be attributable primarily to the interactions of the chemical with tissues at the site of first contact. The absence of enzyme participation in transformations that may potentially lead to toxic events (DNA binding, tissue irritation, etc.) reduces uncertainty in predicting biological activity of formaldehyde across species. There is site concordance among mice, rats and monkeys in the lesions inflicted by formaldehyde under inhalation exposure conditions; and there is apparent similarity between rats and monkeys in the shape of the dose–response curve for both cellular effects and rate of DPX formation. Comparable human data are more limited but do provide indications that the behavior of formaldehyde is consistent with that elucidated in animal experiments. Interactions of formaldehyde with cells result in cellular irritation and destruction, DNA damage, and possible mutations. These mutations, along with cellular proliferation, could lead to the development of cancer, an endpoint that is observed in test animals and for which there is limited evidence in humans.

The mechanisms of formaldehyde-induced carcinogenesis are not completely understood; there is, however, knowledge about some factors which correlate with tumor response and which have plausible roles in cancer development. There is ample evidence that formaldehyde is a mutagen, which is one possible component to the carcinogenicity of formaldehyde. The focus of recent studies on formaldehyde has been on the effects of concentration, total daily dose, and the length of exposure period on various biological endpoints – mucociliary clearance, cell proliferation,

cytotoxicity, DNA-protein binding, and pathology – that may help to explain the pronounced nonlinear carcinogenic response observed in the cancer studies.

Dosimetry data obtained in rats and monkeys were used as alternative means to adjusting exposure concentrations for human subjects to better reflect exposure of the target cells in the nasal epithelium. The use of monkeys as one more suitable animal dosimetric model than rats for human extrapolation finds support in the similarities in anatomic and morphologic structures and breathing pattern to humans. These similarities include the oronasal mode of breathing; comparable relative nasal surface area; mucociliary clearance routes; and inspiratory airflow routes. Conversely, the rat is an obligate nose breather, exhibits a greater relative nasal surface area than humans (or monkeys), shows differences in mucociliary clearance routes, and a different proportion distribution in nasal surface area covered by different epithelia [6]. Anatomical and physiological differences are expected to influence both the rate and pattern of distribution of inhaled formaldehyde. This observation is of particular relevance when applied to formaldehyde which, as described earlier, is expected to react chemically at the site of first contact. Thus, the breathing mode and large relative nasal surface area in the rat would be expected to lead to a high accumulation of formaldehyde in this area, which is consistent with the experimental findings. The oronasal pattern of respiration in humans and monkeys would be expected to reduce the dose of formaldehyde received by the nose and the nasopharynx, and to increase the dose delivered to the oral cavity and upper respiratory tract. This is supported by the observation of a lower DPX formation but more widespread distribution in the respiratory tract of monkeys.

The unit risk estimates for the linearized multistage procedure upper bound (UB) at various exposure levels are presented in Table 2. There is an approximately 6-fold difference between the 1987 rat airborne-based and the 1991 rat dosimetry-based risk estimates (1.6×10^{-2}/ppm versus 2.8×10^{-3}/ppm). An approximate 2.5-fold difference is due to use of DPX as an internal dosimeter in rats. This reflects accommodation of the high-to-low dose nonlinearity in the relation of air concentration to tissue exposure. A 2.5-fold difference from EPA's 1987 assessment is due to a general change in EPA's interpretation of the linearized multistage procedure [6].

Use of the monkey nasal DPX data as a surrogate for human delivered dose would further lower the estimated risk to humans at low exposures (airborne concentrations below 1 ppm) about another 9-fold, yielding an overall 50-fold reduction of unit risk estimates compared to the 1987 unit risk (3.3×10^{-4}/ppm versus 1.6×10^{-2}/ppm).

The human carcinogenic risk estimates based on the monkey DPX data are approximately 10-fold lower than corresponding risks based on rat DPX data at a given formaldehyde exposure concentration. The analysis based on rat DPX data can be interpreted as foregoing the use of the DPX dosimeter for cross-species extrapolation on the grounds that rat–human differences may be poorly illuminated by reference to rat–monkey differences. That is, the unit risk based on rat DPX reflects a correction only for high-to-low dose differences in tissue exposure that results from the apparent saturation of detoxification processes at the high exposure concentrations used in the bioassay.

Although it was recognized that the epidemiologic studies lacked the necessary exposure information to conduct a plausible quantitation of risk, an attempt was made to project limits based on human data that could put risk estimates derived from animal data into perspective. The study by Blair et al. (1986) was used to gauge the behavior of the current risk estimates. The excess deaths attributed to nasopharyngeal cancer are approximately one for each exposure category (range 0.05–89 ppm yr) defined by Blair et al. The corresponding upper bound expected excess lifetime cancer deaths obtained by using the 1991 animal-based unit risk, derived from either rat or monkey dosimetry, are in the range of 10^{-3}–10^{-1}. A number of factors, including the use of cumulative exposure categories, effect modification from exposure to particles, and anatomical and physiological differences among species, modulate the magnitude of this difference. The dose–response functions in humans cannot be firmly established at this time, although based on the chemical characteristics of formaldehyde and dose–response data in animals the dose–response curve for humans is expected to be similar in shape; i.e., relatively shallow at low concentrations followed by a steep increase after an undetermined concentration. The authors recognize the need to develop quantitative risk assessment procedures which further attempt to incorporate biologic data, particularly with regard to pharmacokinetics and mechanism, that yield better estimates of risk.

Use of the monkey DPX data in quantitative risk estimation aims at taking into account not only high-to-low nonlinearity in tissue dose levels, but also dosimetry differences between rodents and primates. Incorporating these dosimetry differences, however, leaves open the question of relative sensitivity of rodents and primates to the toxic effects of formaldehyde. In the absence of any carcinogenic data in monkeys, it is not known how susceptible monkeys are to formaldehyde-induced carcinogenesis. For noncancer effects, the monkeys appear to be more susceptible to formaldehyde toxicity than rats. This is shown by an induction of more widespread histologic lesions in the respiratory tract at equivalent exposure concentrations (6 ppm); however, the relevance of this observation to cancer development is uncertain since not all such lesions develop into tumors. In addition, it is true that a gradient of effects is observed with decreasing exposure concentrations; at 3 ppm cellular changes are confined to the nasal cavity and changes are not observed at concentrations of 1 and 0.2 ppm. This gradient of effects has been reported for both rats and monkeys, and a similar profile is anticipated in humans. Cross-sectional studies of workers in formaldehyde-related industries show higher histological scores (more metaplasia and dysplasia) with longer exposure; unfortunately, only nasal turbinates could be examined. It is difficult to evaluate the full impact of these observations because as stated before, no consistent correlation has yet evolved between nonneoplastic changes and tumor induction. DNA binding also occurs in the lower respiratory tract of monkeys at 6 ppm but it is not measurable at lower exposure concentrations with exception of the nasal area.

The foregoing argument is based on estimates of risk to the nasal epithelium only and may not relate to co-exposures, such as to particulates. Monkeys, as stated above, show DPX formation deeper in the respiratory tract in regions for which rats show neither DPX nor tumor response. Whether these further DPX engender additional

risk, and whether humans are subject to such risk from formaldehyde inhalation is not considered in the present analysis. It is possible that basing risk estimates only on cross-links data corresponding to those in rats for the nose may lead to an underestimate of risk in humans; however, to date DPX-based results do correlate with and seem to provide a rational explanation for the effects observed in test animals. Epidemiologic information provides limited evidence for an association between formaldehyde exposure and cancer of the nasal cavity and nasopharynx but a weaker case is available for the lung. Under the human exposure scenarios considered pertinent to this assessment (airborne concentrations of about 0.3 ppm and lower), the cumulative evidence indicates that areas of the respiratory tract that come in most immediate contact with inhaled formaldehyde are the most likely targets for formaldehyde-induced toxicity. The predicted cancer risk estimates depicted in this document provide a range which encompass epidemiology-based as well as DPX-based estimates. Given the existence of remaining issues to be reconciled, we feel that the incorporation of DPX and other mechanistic considerations in dosimetry determinations is a significant methodological advance in analyses aimed at relating dose–response information generated from animal data to risk projections in humans exposed at low levels.

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Disclaimer

The opinions expressed in this paper are those of the authors. These opinions do not necessarily reflect the position of the US Environmental Protection Agency.

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